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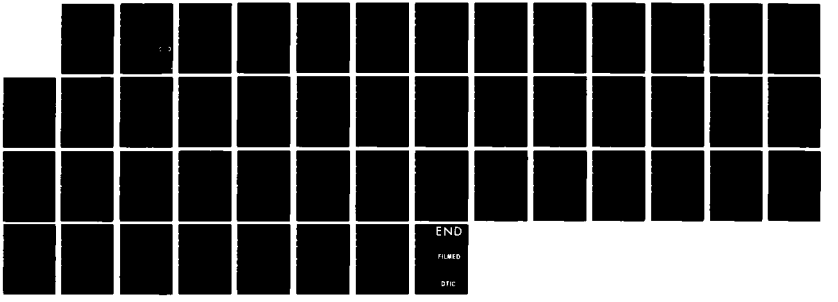

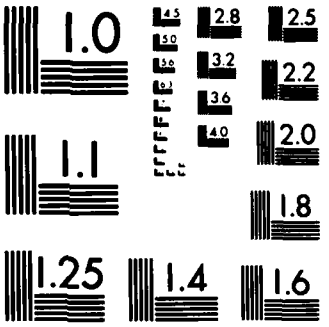

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Synthesis of New Prophylactic Antiradiation Drugs

Annual Report

Ludwig Bauer, Ph.D.

August 1983

(For Period August 1, 1982 through July 31, 1983)

Supported by

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Snythesis of [1-Aryl-2- (or 3-, or 4-_-adamantane]alkylamines, 4-(1-Adamantyl)-benzylamine, N-(w-[1-Aryl-2- (or 3-, or 4-) adamantane]alkyl)-2-mercaptoacetamidines and Derivatives

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This report is divided into four (4) major sections. Each section addresses a phase of the syntheses of adamantyl aryl alkylamines where the amine is incorporated into an N-substituted 2-mercaptoacetamidine, or a derivative of the sulfide function. The first part describes the efforts in the 1-aryl-3-adamantylmethylamine series where the aryl group is 2-thienyl. The next section is devoted to the practical approaches to the synthesis of 1-aryl-2-adamantylalkylamines. The work culminates in the preparation of the first member, namely, 1-phenyl-2-adamantylmethylamine. The third section describes some preliminary

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work on the preparation of 1-aryl-4-adamantylalkylamines. And, the last section reports the synthesis of 4-(1-adamantyl)benzylamines and its conversion to the disulfide based on N-[4-(1-adamantyl)benzyl]-2-mercaptoacetamidine.

FOREWORD

Citations of commercial organizations and trade names in this report do not contribute an official Department of the Army endorsement or approval of the products or services of these organizations.

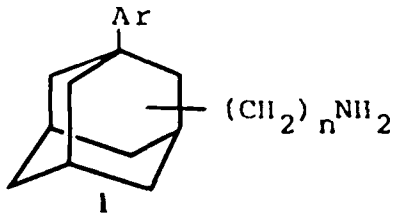
TABLE OF CONTENTS

SYNTHESIS OF NEW PROPHYLACTIC DRUGS:

N-[1-ARYL-2- (OR 3-, OR 4-)-ADAMANTANEALKYL]-2-MERCAPTOACETAMIDINES AND RELATED COMPOUNDS

A. Introduction

The results of our work between 1 August 1982 and 31 July 1983 are presented in this Report. The syntheses are described in several sections appropriately grouped around the chemistry of 1-aryl-2- (or 3-, or 4-) adamantanealkylamines, **1**. The conversion of **1** to the corresponding 2-mercaptoacetamidines **2** (and derivatives thereof), followed previously established methodology[1,2] and is sketched out in **Scheme I.** Details of these syntheses are discussed at appropriate points in this Report.



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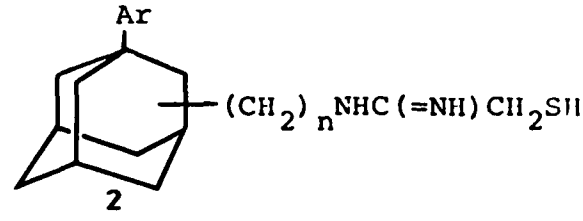


2

B. Synthetic Approaches

1. 1-Aryl-3-adamantanemethylamines and related 2-mercaptoacetamidines

Most of the chemistry in this area has been described fully in Annual Report, August 1982 (1 August 1981 - 31 July 1982). Mercaptans **(9)**, disulfides **(10)**, Bunte salts **(11)**, and phosphorothioates **(8)** based on **2** have been submitted where Ar was 4-methylphenyl, 4-methoxyphenyl, 4-fluorophenyl and 4-methylthiophenyl. Specifically, these compounds are WR 249914, 249915, 249939, 250021, 250022, 250023, 250081, 250282, 250083, 250084. Their full structures are in Table II of August 1982 Report and are repeated as part of their biological evaluations in Tables II

and III of this Report. One new member in this series has been prepared and evaluated. It is the 2-thienyl analog (WR 259393) whose synthesis is described below (**Schemes I and II**).

The Friedel-Crafts reaction of 1-bromo-3-adamantanecarboxylic acid (**3**) with thiophene in the presence of stannic chloride produced a mixture of 1-(2-and 3-thienyl)-3-adamantanecarboxylic acids, **12b** and **13b**, respectively. Gas chromatographic analysis of the esters of these acids indicated that the ratio of 2-and 3-substitution in the thiophene ring was approximately 2:1. Separation of these isomers was attempted via the corresponding amides, **12c** and **13c**. Partial separation of the isomers by means of preparative liquid chromatography made it possible to isolate **12c**. Reduction of **12c** to the amine **12d** provided the precursors for the corresponding mercapto acetamidine **9** (Ar = 2-thienyl). Separation of mixtures of these isomeric amides (**12c, 13c**), the corresponding amines (**12d, 13d**), or, their formamides by various forms of column chroamtography (medium-pressure chromatography[3] or flash chromatography[4]) proved to be extremely tedious and were only marginally successful.

Identification of the isomeric 2- and 3-substituted thiophenes, was possible only by means of proton nuclear magnetic resonance spectrometry (^{1}H NMR) at high fields. At 60 MHz, the three ring protons in **12** or **13** showed an ABC pattern. However, at 180 MHz, the pattern changed to AMX, and the three ring protons in each isomer showed a pattern approaching first order, each signal consisting of a doublet of doublets. However, the relatively close values of the chemical shifts and coupling constants required some established model compounds. The Friedel-Crafts substitution of thiophene by 1-adamantyl bromide has been reported.[5,6] There were isolated **12a** and **13a** which were partly separated and their ^{1}H NMR spectral patterns at 180 MHz were established (Table I). The ^{1}H NMR parameters of **12a, 13a** served as a model for the corresponding carboxamides, **12c** and **13c**

(Table I). By means of tedious chemical methods, it had been possible to separate isomers **12a** and **13a**.[5,6] These were converted to chloromercuri derivatives, which were separated by fractional crystallization. Protolysis of the pure chloromercuric derivatives regenerated pure **12a** or **13a**.[5] To prove the structure of each pure isomer, **12a** and **13a** were desulfurized by Raney Ni to 1-(n-butyl)- and 1-(sec-butyl)adamantane, respectively.[5] Unfortunately, chloromercuration of the carboxamido analogs, **12c** and **13c**, yielded solid chloromercuri derivatives which could not be separated satisfactorily by fractional crystallization. Nor, was the Raney Ni desulfurization clean-cut. In the end, preparative liquid chromatographic separation yielded pure **12c** which was identified by its ^{1}H NMR spectrum. Reduction of amide **12c** yielded the amine **6** (Ar = 2-thienyl) which was converted by means of methyl chloroacetimidate (generated in situ from chloroacetonitrile and methanol) and HCl to the chloroacetamidinium salt, **7**. The phosphorothioate **8** obtained from **7** and sodium phosphorothioate could not be purified sufficiently to produce an acceptable analytical sample. Hence, **8** was hydrolyzed by dilute hydrochloric acid to the mercaptan **9** (Ar 2-thienyl) which was submitted and evaluated as WR-250393.

2. Approaches to the synthesis of 1-aryl-2-adamantanemethylamines

The synthesis of a number of suitable 1,2-disubstituted adamantanes is plausible via the protoadamantane route. The literature preparation of 4-protoadamantanone, **15**, from 1-adamantanol, **14** was reproducible[7] and the mechanism of formation is described in **Scheme III**. The ketone **15** readily adds organometallic reagents to form 4-alkyl or 4-aryl-4-protoadamantanols, **16**.[8-10] Rearrangement of **16** with acidic reagents, H^+X^-, leads to 1,2-disubstituted adamantanes of type **18**, where the alkyl or aryl group R is at position 1 and the nucleophilic group X^- ends

up at position 2.[47] Such a rearrangement of **16** by HX can be imagined to proceed via the carbocation of **17.**

Addition of phenyllithium or phenylmagnesium bromide to **15** furnishes 4-phenyl-4-endo-protoadamantanol, **19a** and 4-phenyl-4-exo-protoadamantanol, **19b.**[7,8] No attempt was made to separate the stereoisomers **19.** One had to be extremely careful not to bring acidic reagents near **19** to avoid the elimination of water to form the alkene **21.** For example, when the reaction mixture from the organometallic reagent was decomposed and remained in contact with ammonium chloride, the alkene **21** rather than **19** was the product. However, **21** would also rearrange to the adamantane skeleton when exposed to strong acids. For example, the reaction of **21** with HBr yielded **20b.**

Attempts to carry out a Grignard synthesis of 1-phenyl-2-adamantanecarboxylic acid from **20b** proved to be disappointing. Reaction with good quality magnesium yielded only the starting material, **20b.** Extremely high grade magnesium (followed by CO_2), produced 1-phenyladamantane, **22,** (98%). Such a reduction is expected in view of a recent paper by Molle et al.[11] These authors reported that in the absence of mechanical stirring, 2-bromoadamantane could form a Grignard reagent in ether in the presence of $BrCH_2CH_2Br$ (about 60% yield) but upon workup the major product was 2,2'-biadamantane (35%) and 2% adamantane. These authors reported that carbonation of the Grignard reagent formed 2-bromoadamantanecarboxylic acid in 50% yield.[11] When comparing their results with ours from 1-phenyl-2-bromoadamantane, it could be that the neighboring phenyl group in the Grignard reagent from **20b** influences the course of the Grignard reaction. It had also been reported that the Grignard reaction on 1-bromoadamantane gave only 1,1'-biadamantane.[5]

Alternate methods were sought to introduce a carbon fragment at the 2-position of **20.** A logical reaction would appear to be a nucleophilic displacement

reaction of a bromide or sulfonate by cyanide ion. However, the reaction of **20b** with KCN in the presence of phase transfer catalysts gave back the starting material, quantitatively. The next attempt to form the nitrile was *via* the corresponding known p-toluenesulfonate, **25** and such an attempted displacement also was unsuccessful. The sulfonate **25** was made by rearranging **19** with formic acid to the formate, **(23)**. Hydrolysis of this ester produced the alcohol **24**, which was reacted with p-toluenesulfonyl chloride (TsCl) to afford **25**[8] **(Scheme IV)**.

Finally, 1-phenyl-2-adamantanol, **24**, was reacted with trimethylsilyl chloride, sodium iodide, sodium cyanide in acetonitrile and DMF according to a new procedure to convert alcohols directly to nitriles.[10] In spite of the fact that nitriles were obtained from cyclohexanol (16%), cholesterol (85%), 1-adamantanol, (91%), we could not effect this conversion in our system, even by going to very long reaction times.

Therefore, other methodology was sought (Scheme **IV**). The alcohol, **24**, was oxidized readily by Jones' reagent (chromic oxide in sulfuric acid) to furnish the ketone, **26** in acceptable yields.[26] Using the Leusen reagent,[12] the ketone was converted to the nitrile, **27** in 65-70% yield. The mechanism of this conversion is rather complex and has not been settled. This "reductive cyanation" is believed to proceed primarily by the mechanism shown in **Scheme V.** The by-products of the reaction are p-toluenesulfinic acid and alkyl formates. Without discussing all of the ramifications and some of the evidence which supports this complex mechanism, suffice it to state that in the base-catalyzed reaction commences when nucleophilic addition of the active methylene groups of the isocyanide sulfone to the ketone to form eventially an oxazoline, which can open up to ketenimine derivative. Alcoholsis of the formyl group leads eventually to the required nitrile.

Reduction of the nitrile **26** with either lithium aluminum hydride ($LiAlH_4$) or diborane-dimethyl sulfide complex according to the method of Brown and

coworkers[13,14] did not give us the expected amine, **30**. Instead, a good yield of the symmetrical secondary amine, **28** was formed.

We then turned to the addition of water to the nitrile (base and hydrogen-peroxide catalyzed) to form the amide, **29**.[15] The amide was characterized and reduced by $LiAlH_4$ to form the primary amine, **30**. The incorporation of this amine into the 2-mercaptoacetamidine system is under study.

Another approach to the 1,2-disubstituted adamantane system utilized the following rationale. The reaction of 4-protoadamantanone with dimethylsulfoxonium methide yielded a mixture of the endo- and exo-epoxides, **31**.[8,16] It was planned to react these epoxides with organometallic reagents. To ensure that ring opening would proceed unilaterally via the best carbocation, some $AlCl_3$ was added to the reaction mixture. It was hoped that the reaction of **31** with ArMgX would be along one of two paths. Path A might have $AlCl_3$-catalyzed ring-opening to give the tertiary carbocation which might rearrange to the less strained secondary (2-adamantyl) carbocation and then be neutralized by the organometallic reagent to give the alcohol **32**. Such an alcohol should be a logical precursor to the primary amine **33**. Alternatively (Path B), the organometallic reagent might react directly with the epoxide to form the tertiary alcohol **34** which should rearrange quickly during the reaction, or afterwards with acids to give **35**. The reaction of **31** with phenyllithium or phenylmagnesium bromide and $AlCl_3$ to gave a complex mixture of reaction products, which have not been resolved to date. However, none of the expected products could be readily retrieved from this mixture. In view of the recent paper on successful reactions of Friedel-Crafts reactions of some epoxides with activated arenes to form aryl alcohols,[17] it was hoped to apply such a reaction to our system. There should have been formed **37** and/or **38**. The reaction of **31** with anisole in the presence of $SnCl_4$, the only product which was isolated was the known diol, **36**, apparently a product due to hydrolysis of **31**, probably

formed during work-up. Preliminary products from another reaction of 31 with toluene and $AlCl_3$ again gave at least 2 products as judged from TLC and spectral data. Much further work is needed in this area.

3. Approaches to the synthesis of 1-aryl-4-adamantanemethylamines (Scheme VII)

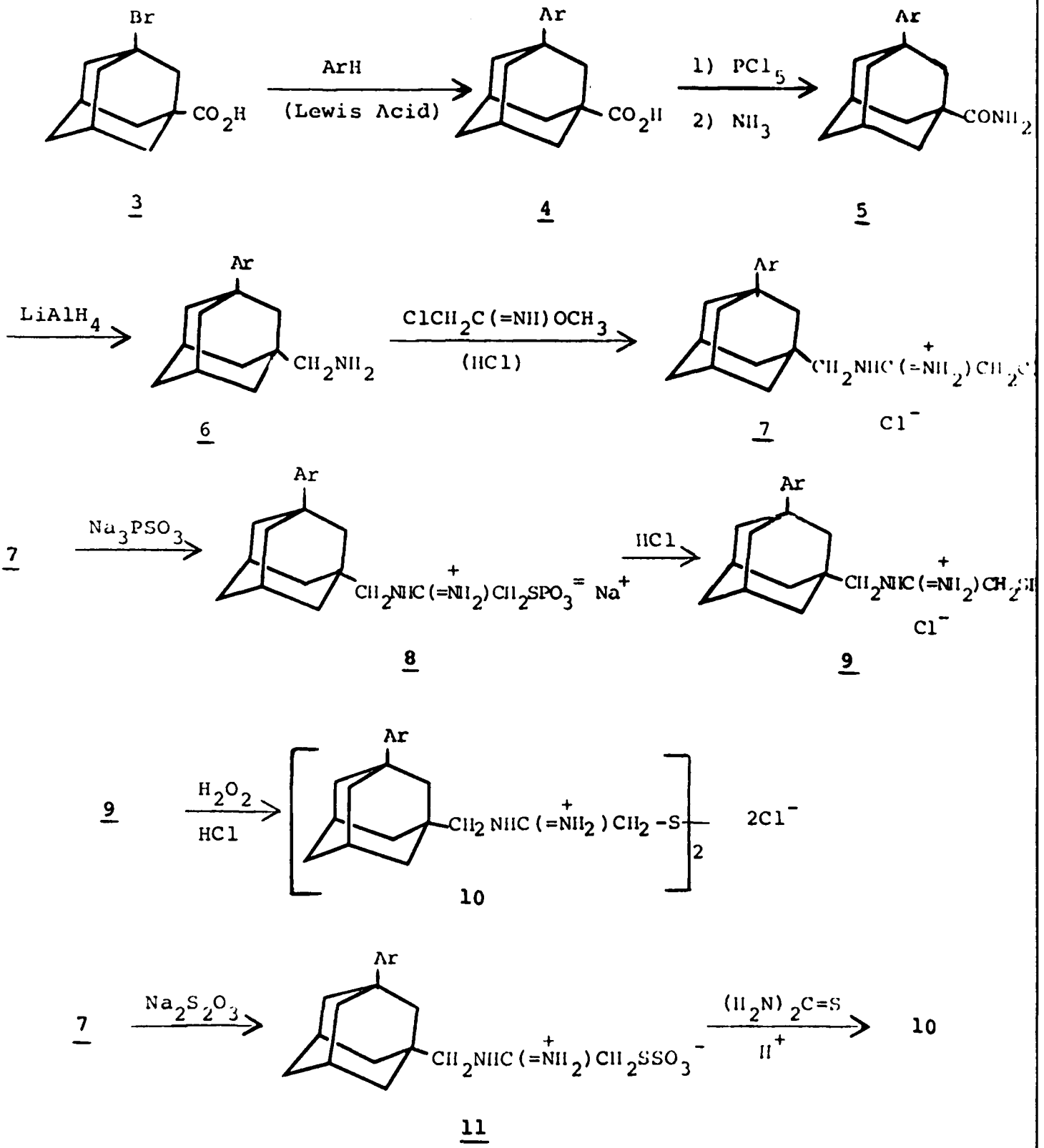
Exploratory work towards the 1,4-system followed the following approach. Bromination of adamantanone, 39, in the presence of $AlBr_3$ in an improved procedure[18] yielded 1-bromo-4-adamantanone, 40. Friedel-Crafts reaction with benzene ($AlCl_3$) had been reported[19] and yielded 1-phenyl-4-adamantanone. A cognate Friedel-Crafts alkylation with toluene in our laboratory produced the 1-(4-methylphenyl)-4-adamantanone, 41. Reductive cyanation converted this ketone to a mixture of nitriles, 42. The nitriles were reduced by $LiAlH_4$ to the corresponding methylamines, 43. Separation and characterization of the isomers of 43 needs to be addressed before these are incorporated as the amino constituent of a subsequent 2-mercaptoacetamidine (see Scheme I).

4. Synthesis of 4-(1-adamantyl)benzylamines and the disulfide based on N-(1-adamantyl)benzyl-2-mercaptoacetamidine (Scheme VIII)

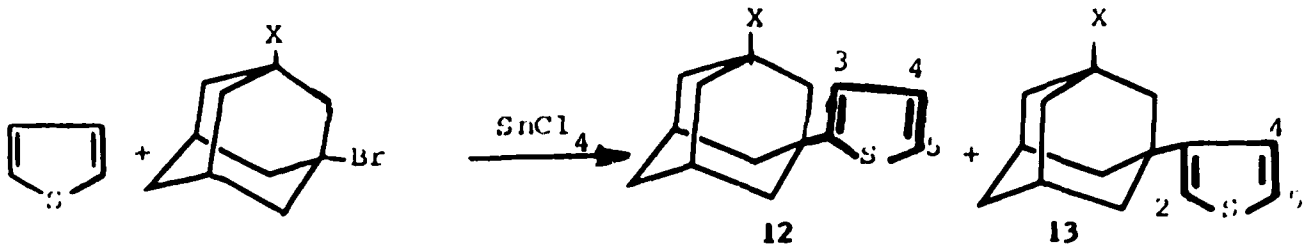
To explore the effect of separating the lipophilic adamantane ring from the highly polar amidine group, a member of a possible series of ω-[4-(1-adamantyl)-phenyl]alkylamines was prepared. The initial member was the simplest in such a series, namely the benzylamine derivative, 44. Repeating the known Friedel-Crafts alkylation[20] of bromobenzene with 1-bromoadamantane, 4-(1-adamantyl)bromobenzene was obtained.

Using the standard Grignard method for the preparation of the acid, and subsequent conversion to the amine, it was possible to obtain 44 in good yield.

Scheme I


Br
CO2H
ArH
(Lewis Acid)
Ar
CO2H
1) PCl5
2) NH3
Ar
CONH2
3
4
5
LiAlH4
Ar
CH2NH2
ClCH2C(=NH)OCH3
(HCl)
Ar
CH2NHC(=NH2)CH2Cl
Cl−
6
7
7
Na3PSO3
Ar
CH2NHC(=NH2)CH2SPO3= Na+
HCl
Ar
CH2NHC(=NH2)CH2Cl
Cl−
8
9
9
H2O2
HCl
Ar
CH2NHC(=NH2)CH2-S-
2
2Cl−
10
7
Na2S2O3
Ar
CH2NHC(=NH2)CH2SSO3−
(H2N)2C=S
H+
10
11

Scheme II



a X=H
b $X=CO_2H$
c $X=CONH_2$
d $X=CH_2NH_2$

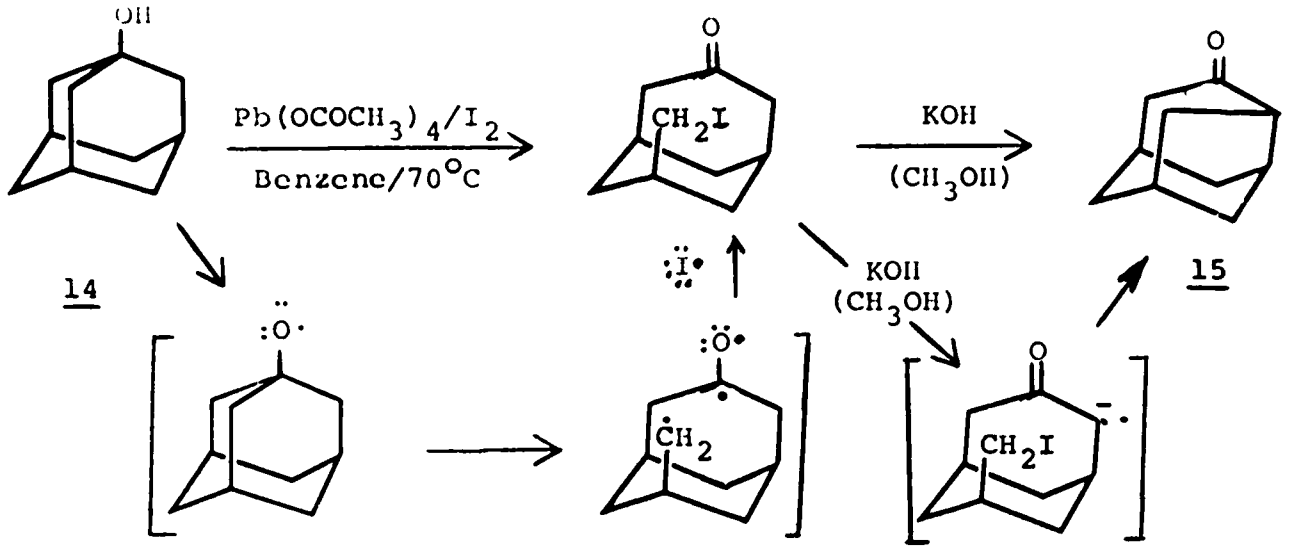
a X=H
b $X=CO_2H$
c $X=CONH_2$
d $X=CH_2NH_2$

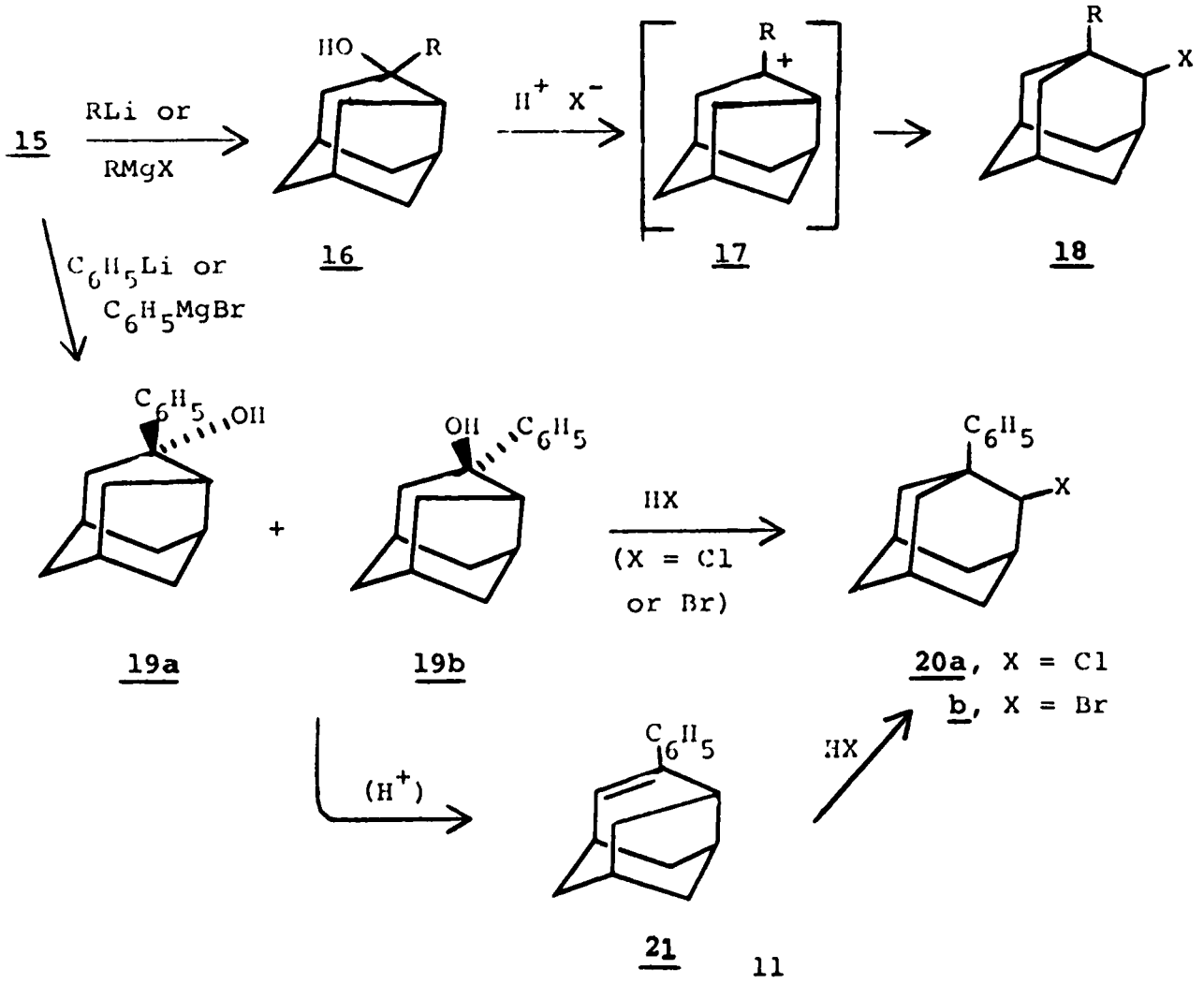
Table I. ^1H NMR Spectral Characteristics of **12** and **13** in $CDCl_3$

Compound	*Chemical Shifts (ppm)* downfield from tetramethylsilane				Coupling Constants (Hz)				
	H-2	H-3	H-4	H-5	$J_{2,4}$	$J_{2,5}$	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
12a*	--	6.80	6.92	7.10	--	--	3.6	1.2	5.1
12c	--	6.75	6.84	7.01	--	--	3.6	1.2	5.1
13a*	6.86	--	7.02	7.17	1.2	3.0	--	--	5.1
13c	6.88	--	7.00	7.18	1.2	3.0	--	--	5.1

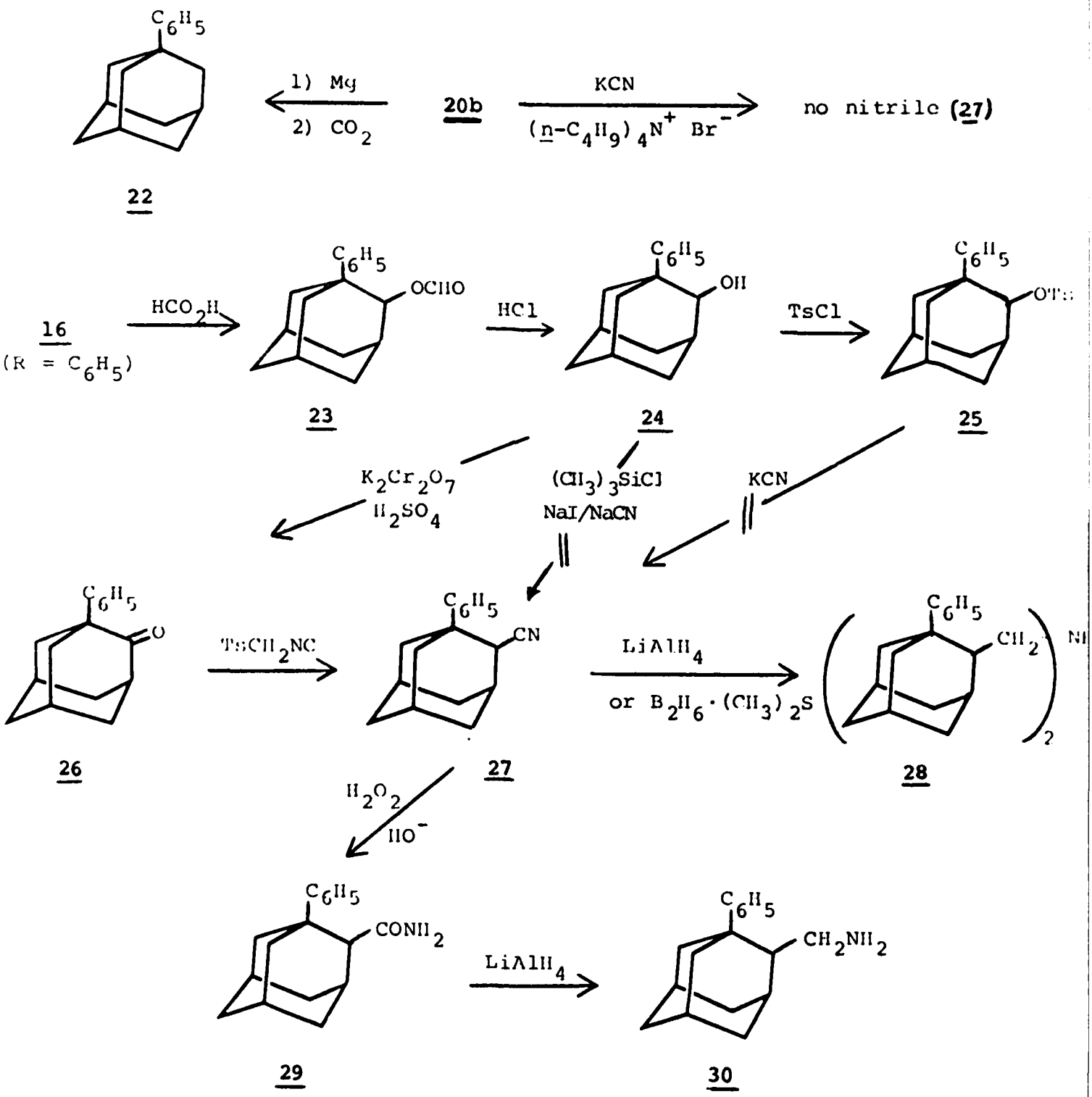
*Lit. values for the chemical shifts of **12a** (CCl_4) are 6.65 to 7.05 ppm and that for **13a**, 6.80 to 7.20 (Ref. 4,5).

Scheme III

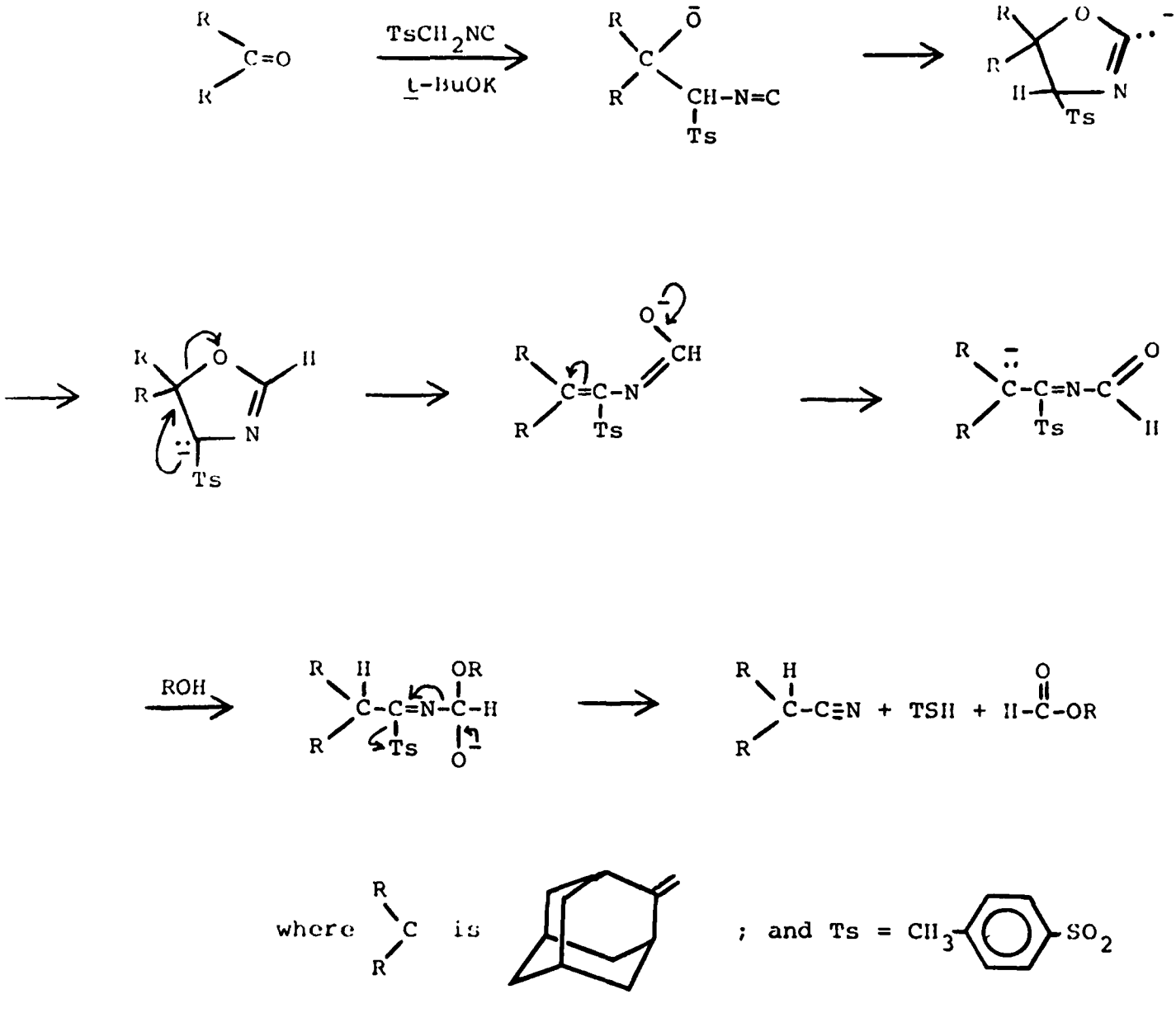

OH
Pb(OCOCH3)4/I2
Benzene/70°C
O
CH2I
KOH
(CH3OH)
14
15
KOH
(CH3OH)
CH2


15
RLi or
RMgX
HO
R
16
H+ X-
R
+
17
R
X
18
C6H5Li or
C6H5MgBr
C6H5
OH
19a
+
OH
C6H5
19b
HX
(X = Cl
or Br)
C6H5
X
20a, X = Cl
b, X = Br
(H+)
C6H5
21
HX

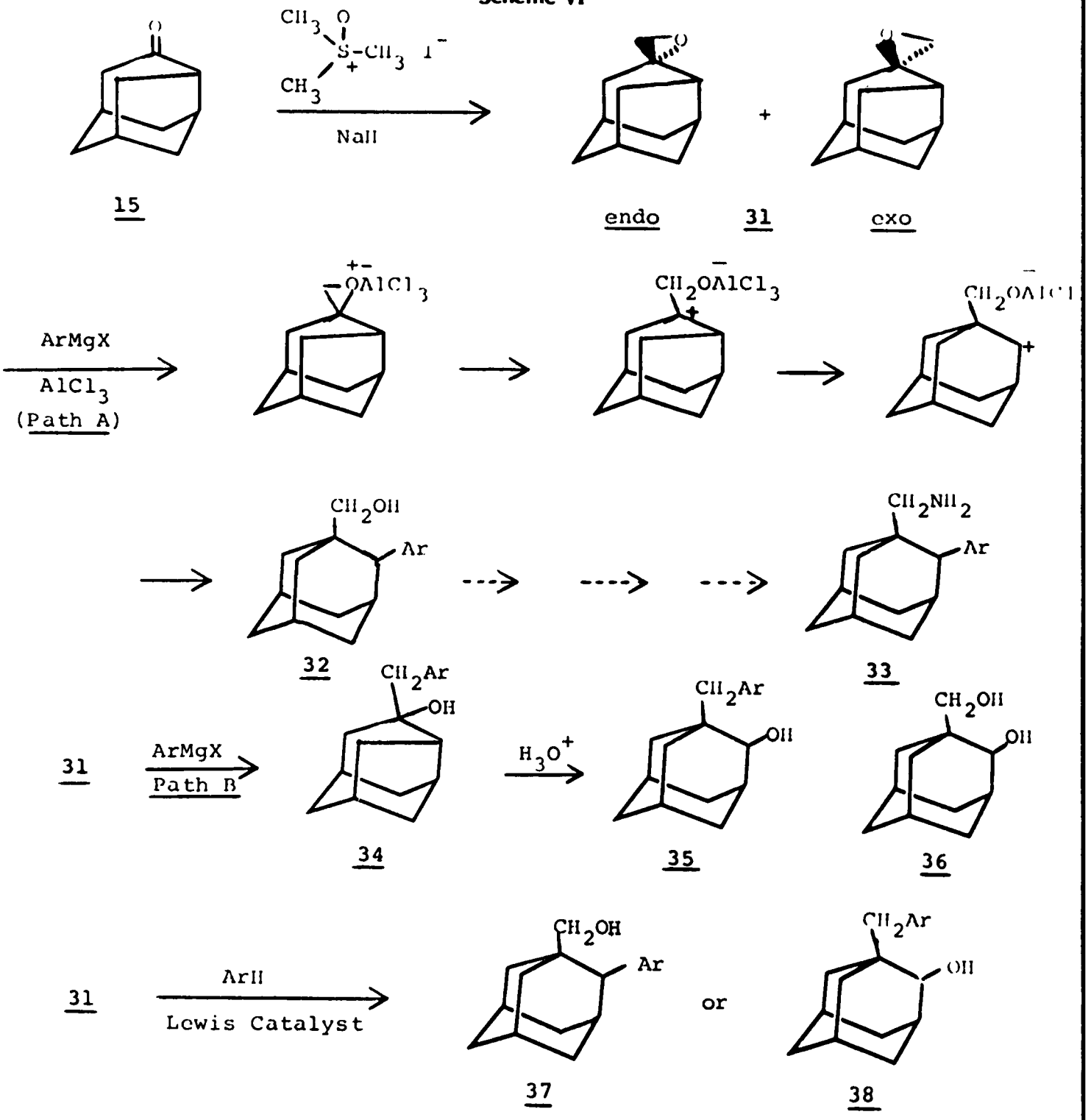
Scheme IV


C6H5
1) Mg
2) CO2
20b
KCN
(n-C4H9)4N+ Br-
no nitrile (27)
22
16
(R = C6H5)
HCO2H
OCHO
HCl
OH
TsCl
OTs
23
24
25
K2Cr2O7
H2SO4
(CH3)3SiCl
NaI/NaCN
KCN
O
TsCH2NC
CN
LiAlH4
or B2H6·(CH3)2S
CH2
NH
2
26
27
28
H2O2
HO-
CONH2
LiAlH4
CH2NH2
29
30

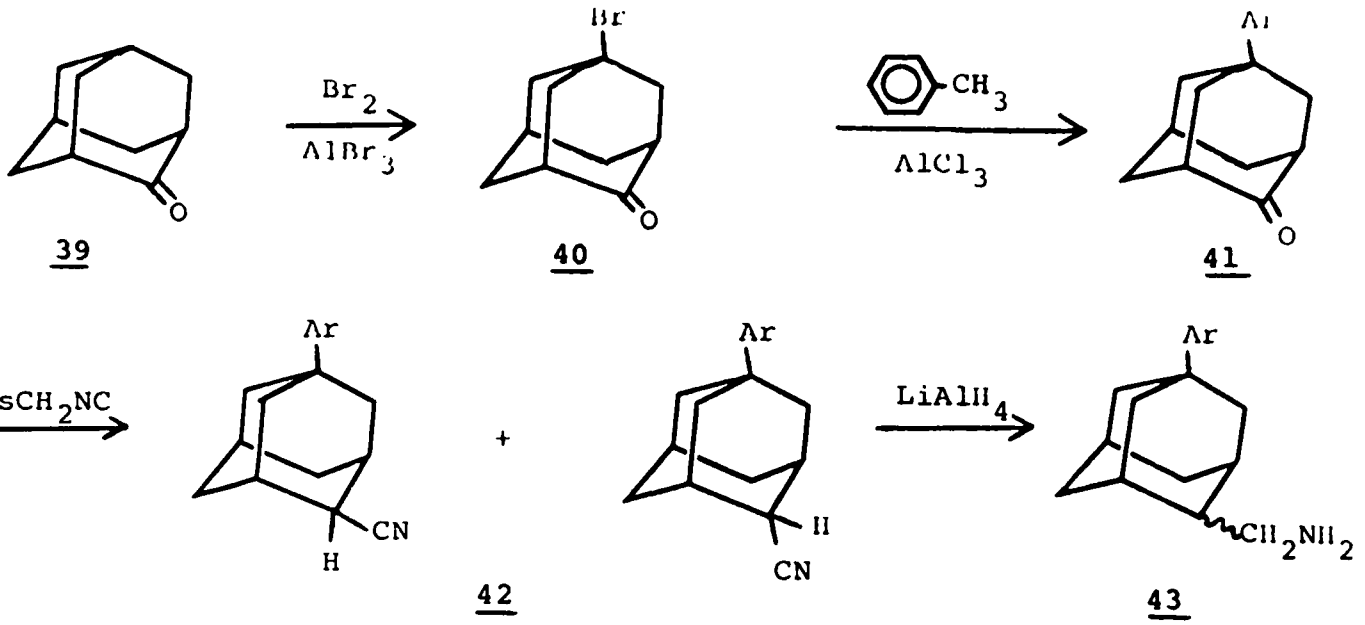
Scheme V



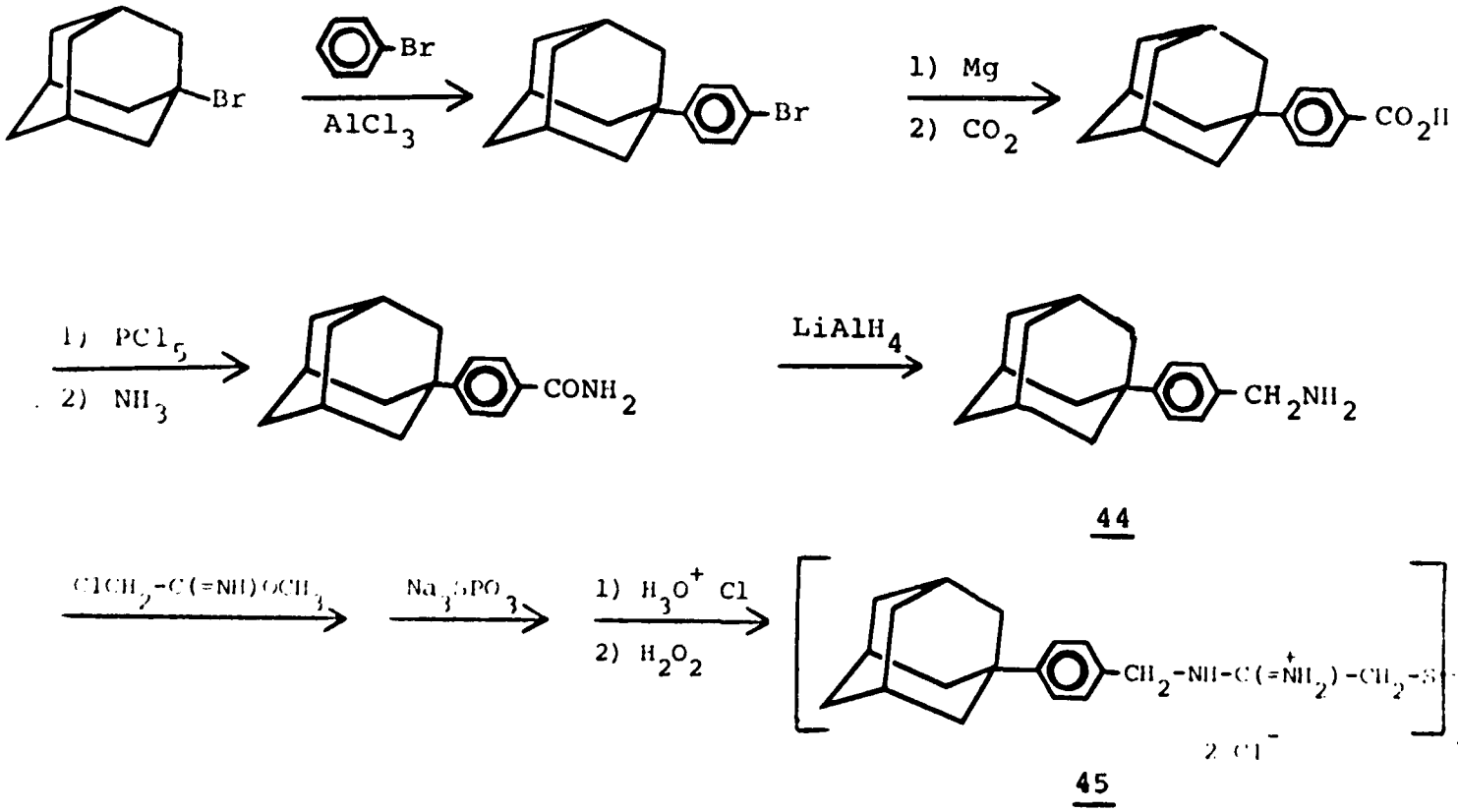
Scheme VI


15
NaH
endo
31
exo
ArMgX
AlCl3
(Path A)
32
33
31
ArMgX
Path B
34
H3O+
35
36
31
ArH
Lewis Catalyst
37
or
38

Scheme VII



Scheme VIII



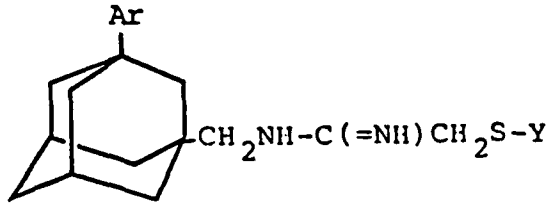
When this primary amine was treated with methyl chloroacetimidate, HCl, and then sodium phosphorothioate (**Scheme I**), an impure amidinium phosphorothioate was obtained. Even the resulting mercaptoacetamidine was difficult to handle, so we prepared the stable disulfide as the first member in this series for testing (WR 205394).

5. Biological evaluation of testing data to date

Tables II and III list the "Acute Toxicities" and "Radioprotectant Activity" in mice of the compounds submitted from this laboratory. While not complete, the data points up the relative toxicity of these compounds but there is radioprotective activity. The Bunte salt group (SSO_3H) has been dropped and our efforts concentrate on the synthesis of phosphorothioate (SPO_3H_2), thiol (SH) and disulfides (-SS-) derivatives of 2-mercaptoacetamidines, in that order.

No definite conclusions can be reached with the biological data on hand, at present. It is hoped that additional examples will help to bring about the creation of a less toxic radioprotectant.

Table II: Summary of Acute Toxicity in Mice (ip Administration)



WR-No	Ar	Y	Mol. Formula (Mol. Weight)	Vehicle	Dose* mg/kg	Deaths	30-Day Survivors, %
249,939	4-methyl-phenyl	SO_3H	$C_{20}H_{28}N_2O_3S_2$ (408.22)	20% EtOH-Tween 80	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	5/5	0
					37.5	5/5	0
					18.75	3/5	40
					9.38	0/5	100
250,021	4-methoxy-phenyl	disulfide (2 HCl)	$C_{40}H_{56}Cl_2N_4O_2S_2$ (759.46)	20% EtOH-Tween 80	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	5/5	0
250,022	4-methoxy-	PO_3HNa	$C_{20}H_{28}N_4O_4PSNa$	20% EtOH-	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	3/5	40
250,023	4-methoxy-phenyl	H (HCl)	$C_{20}H_{29}ClNOS$ (380.73)	10% EtOH-Tween 80	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	5/5	0
					37.5	5/5	0
					18.75	3/5	40
					9.38	0/5	100

Table II Continued: Summary of Acute Toxicity in Mice (ip Administration)

NSC-No	Ar	Y	Mol. Formula (Mol. Weight)	Vehicle	Dose* mg/kg	Deaths	30-Day Survivors,
250,281	4-methyl-thiophenyl	SO_3H	$C_{20}H_{28}N_2O_3S_3$ (440.22)	20% DMSO-80% water	120	3/5	40
					60	1/5	80
					30	0/5	100
					15	0/5	100
				Klucel	120	1/5	80
					60	0/5	100
					30	0/5	100
250,282	4-methyl-thiophenyl	PO_3HNa	$C_{20}H_{28}N_2O_3PO_3Na$ $3\ H_2O$ (516.27)	20% EtOH-20% Emulphor 60% Saline	102	5/5	0
					51	0/5	100
					25.5	0/5	100
					12.75	0/5	100
250,393	2-thienyl	H (HCl)	$C_{17}H_{25}ClN_2S_2$ (356.70)	20% EtOH-80% water	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	5/5	0
					37.5	5/5	0
250,394	for structure see below**	disulfide (2 HCl)	$C_{38}H_{52}Cl_2N_4S_2$ (699.42)	20% EtOH-80% water	600	5/5	0
					300	5/5	0
					150	5/5	0
					75	0/5	100

*Drug dosage is expressed in mg/kg and is corrected for salt and water content.

**Structure is $[4\text{-}(1\text{-Adm})C_6H_4CH_2NH\text{-}C(=NH)CH_2S]_2$ 2 HCl, where 1-Adm is 1-adamantyl.

Table III Continued: Radioprotectant Activity in Mice

WR-No	R	Y	Mol. Formula (Mol. Weight)	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
250,023	OCH_3	H (HCl)	$C_{20}H_{29}ClN_2OS$ (380.73)	16 8 4 2		50 30 0 0
250,281	SCH_3	SO_3H	$C_{26}H_{28}N_2O_3S_3$ (440.22)	60 30 15	1/10 0/10 0/10	50 60 50
250,083	F	PO_3HNa	$C_{19}H_{25}FN_2O_3PSNa$ — 1.5 H_2O (461.22)	36 18 9	6/10	40 60 80
250,082	SCH_3	PO_3HNa	$C_{20}H_{28}N_2O_3PSNa$ 3 H_2O (576.27)	60 30 15	1/10 0/10 0/10	70 70 30
250,084	F	disulfide (2 HCl)	$C_{38}H_{50}F_2Cl_2N_4S_2$ (735.40)	36 18 9	10/10 8/10	0 20 80

*Drug doses expressed as mg/kg corrected for salt and/or water content and were administered ip 30 minutes prior to radiation.

**Percent of mice surviving at 30 days after treatment with drug and whole-body irradiation of 1000 rads ($LD_{100/30}$).

Table III Continued: Radioprotectant Activity in Mice

WR-No	R	Y	Mol. Formula (Mol. Weight)	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
250,023	OCH_3	H (HCl)	$C_{20}H_{29}ClN_2OS$ (380.73)	16 8 4 2		50 30 0 0
250,028	SCH_3	SO_3H	$C_{26}H_{28}N_2O_3S_3$ (440.22)	60 30 15	1/10 0/10 0/10	50 60 50
250,032	F	PO_3HNa	$C_{19}H_{25}FN_2O_3PSNa$ 1.5 H_2O (461.22)	36 18 9	6/10	40 60 80
250,082	SCH_3	PO_3HNa	$C_{20}H_{28}N_2O_3PSNa$ 3 H_2O (576.27)	60 30 15	1/10 0/10 0/10	70 70 30
250,084	F	disulfide (2 HCl)	$C_{38}H_{50}F_2Cl_2N_4S_2$ (735.40)	36 18 9	10/10 8/10	0 20 80

*Drug doses expressed as mg/kg corrected for salt and/or water content and were administered ip 30 minutes prior to radiation.

**Percent of mice surviving at 30 days after treatment with drug and whole-body irradiation of 1000 rads ($LD_{100/30}$).

Experimental Section

Melting points are uncorrected and were determined on a Thomas Hoover apparatus up to 240 °C and for compounds melting over 240 °C on a Mel-Temp apparatus. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Proton (^{1}H) NMR spectra were obtained at 60 MHz on a Varian T60A spectrometer equipped with a Nicolet TT-7 Fourier Transform Accessory and at 180 MHz on a 180 MHz Bruker CPX-180 instrument. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. The abbrevations, br, s, d, t and m refer to broad, singlet, doublet, triplet, and multiplet, respectively. Adamantane proton resonances were not resolved and usually appeared as broad multiplets between 1.5 and 2.3 ppm.

Mass spectra (MS) were obtained by Mr. Richard Dvorak at 70 eV on either a Perkin-Elmer Hitachi RMU7 or Varian MAT 112 spectrometer. The ions which are listed are those with m/e greater than 100 and in general with intensities greater than 20% of the base peak, unless otherwise deemed important. Relative intensities are recorded as percentages of the base peak and are shown in parentheses.

IR spectra were recorded on a Nicolet MX-1 FT IR spectrophotometer.

Thin layer chromatograms (TLC) were developed on 8 x 4 cm slides coated with silica gel containing a fluorescent indicator (Eastman Chromagram Sheets, No. 6060). Spots were visualized by UV light and/or exposure to iodine vapor. The general statement "that solvents were removed or distilled in vacuo", implies that solvents were evaporated, in vacuo, usually of a rotary flash evaporator using a hot water bath (40-90 °C; 20-30 Torr). All pure samples were dried at room temperature, in vacuo, over $CaCl_2$ or P_2O_5.

Silica gel for regular column chromatography was purchased from J.T. Baker Chem. Co., Phillipsburg, NJ (60-200 mesh) and for medium pressure or flash chromatography was that of E. Merck's Kieselgel 60 (230-400 mesh ASTM).

All chemicals and solvents were used as purchased, unless otherwise stated. The ^{1}H NMR spectra of all reagents were obtained prior to use to ensure their purity. Petroleum ether refers to that fraction bp 30-60 ^{o}C.

Starting materials

Chloroacetonitrile, 1-bromoadamantane, was purchased from Aldrich Co., Milwaukee, Wisconsin. Trisodium phosphorothioate was made from thiophosphoryl chloride (obtained from Alfa Products, Danver, Ma, 01923) by reaction with sodium hydroxide, according to the method of Akerfeldt.[20]

1. Syntheses Leading To 1-Aryl-2-adamantanemethylamines

1-Adamantanol. This hydrolysis was carried out according to the method of Geluk and Schlatmann.[21] A mixture of bromoadamantane (20 g, 0.093 mol), HCl (0.67 N, 200 ml) and dimethylformamide (26 ml) were stirred at 105 ^{o}C for 0.5 h. The reaction mixture was diluted with water (200 ml) and filtered. The solid was washed several times with water and dried, in vacuo. The solid weighed 13 g (92%), mp 272-274 ^{o}C (sealed capillary, sublimes, lit.[21] mp 283-285 ^{o}C); TLC, R_f 0.69 ($CHCl_3$-C_2H_5OH, 5:1) showing the absence of 1-bromoadamantane, R_f 0.89; ^{1}H NMR ($CDCl_3$) δ 1.46 (br s, OH), 1.62-2.14 (m, Ad H).

4-Protoadamantanone. A 2-L three-necked flask was equipped with an efficient mechanical stirrer and a reflux condenser and charged with dry benzene (600 ml). The flask was placed in a water bath and stirring initiated, and lead tetraacetate (58.3 g, 0.132 mol), iodine (37.4 g, 0.147 mol) and 1-adamantanol (10.0 g, 0.066 mol) were added. The reaction mixture turned dark red. The bath temperature was gradually raised to 80 ^{o}C over a 20 min period and was then allowed to cool to 70-75 ^{o}C. Stirring was continued for 2 h at 70-75 ^{o}C and for an additional 1 h while the mixture was cooled to room temperature. Inorganic salts

were filtered off and carefully washed with ether (5 x 50 ml). The benzene filtrate and ether washings were combined in a 2-L separatory funnel and shaken with saturated aqueous sodium bisulfite (500 ml) until the dark red color disappeared. The layers were not separated. If the color reappeared within 10-15 min, the mixture was shaken again until colorless. The procedure was repeated as many times as necessary. The layers were then separated and the organic layer was washed with water (500 ml) and saturated sodium bicarbonate (250 ml). The benzene-ether solution was dried ($MgSO_4$) for 1 h and concentrated in a round bottom flask (500 ml) with a rotary evaporator at a bath temperature of 40-50 °C. The last 40 to 50 ml were removed without heating. The resulting crude, oily iodo ketone was used immediately as it is thermally unstable and in the absence of solvent the decomposition is rapid, even at room temperature.

The flask containing the iodo ketone is equipped with a magnetic stirring bar and a reflux condenser. A solution of potassium hydroxide (7.0 g, 0.125 mol) in methanol (150 ml) was added and the mixture was stirred and heated under reflux for 3 h. The contents of the flask were allowed to cool to room-temperature and poured onto ice-water (300 ml). The resulting mixture was extracted with ether (5 x 100 ml). The combined extracts after washing with water (100 ml) were dried (Na_2SO_4) and evaporated under reduced pressure leaving a yellow solid (8.5 g). A solution of this crude product in chloroform (3 ml) was passed through a column packed with neutral alumina (activity III, 200 g). The column was eluted first with pentane (150 ml) and then with ether-pentane (3:7 v/v, 500 ml) and 25 ml fractions were collected and analyzed by gas chromatography (OV 225, 140 °C, retention time 7 min) and fractions with 98% or more purity were combined and evaporated affording 4-protoadamantanone (7.3 g, 72%) as a pale yellow solid, mp 202-204 °C. The ketone was recrystallized from methanol which raised the mp to 206-210 °C (lit.[7] mp 207-210°C); ^{1}H NMR ($CDCl_3$) δ 1.01-2.92 (a series of complex m).

4-Phenyl-4-protoadamantanol. Phenylmagnesium bromide was prepared by refluxing a mixture of bromobenzene (2.5 g, 0.016 mol), magnesium turnings (0.35 g, 0.015 mol) and anhydrous ether (40 ml) for 2 h (or until most of the magnesium had dissolved). A solution of 4-protoadamantanone (2 g, 0.013 mol) in anhydrous ether (20 ml) was added dropwise and the reaction mixture refluxed for 2 h, cooled, treated with saturated ammonium chloride solution (10 ml) and extracted with ether (3 x 25 ml). Ether extracts were washed well with saturated sodium bicarbonate solution (2 x 50 ml) and then with water (50 ml). The extract was dried (Na_2SO_4) and evaporated, in vacuo, at room temperature, to furnish a waxy solid (2.0 g, 67%) mp 83-84 °C; (lit.[8a] mp 84-85 °C); ^{1}H NMR (CCl_4) δ 1.14-2.82 (m, Ad H), 7.10-7.55 (m, ArH).

The same product was obtained in similar yield when phenyllithium was used. This alcohol is extremely sensitive to elimination by acidic reagents.

4-Phenylprotoadamantene. A solution of 4-phenyl-4-protoadamantanol (2.0 g) in HCl (5 N, 20 ml) was stirred at room temperature for 30 min. The mixture was diluted with water (100 ml), and extracted with ether (3 x 30 ml). The extract was dried (Na_2SO_4) and solvents evaporated. The residue was chromatographed on a column of silica gel (100 g) and was eluted by petroleum ether-ethyl acetate (19:1) to give the alkene (1.6 g, 88%) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.1-3.15 (H-3), 6.49 (dd, H-5, J=7.8, 1.8 Hz), 7.0-7.61 (m, Ar H).

1-Phenyl-2-bromoadamantane. 4-Phenylprotoadamantene (1.05 g, 0.005 mol) was refluxed with HBr (48%, 10 ml) for 2 h, cooled, the mixture diluted with water (100 ml), and extracted with ether (3 x 25 ml). The ether extract was washed with water and dried (Na_2SO_4). Solvents were evaporated and the residue was chromatographed on silica gel (40 g). Elution with petroleum ether gave 1-phenyl-2-bromoadamantane (1.08 g, 75%) mp 80-81 °C; TLC ^{1}H NMR ($CDCL_3$) δ 1.49-2.65 (m, adamantane Hs), 4.84 (br s, CHBr), 7.30 (s, ArH); MS m/e, 292 (10), 290 (10),

MS (70eV, rel int) 292 (25) 129 (15). Anal. Calcd. for $C_{16}H_{29}Br$: C, 65.94; H, 6.57. Found: C, 66.05; H, 6.65.

1-Phenyl-2-chloroadamantane. 4-Phenylprotoadamantene (1.05 g, 0.005 mol) was refluxed with conc. HCl (10 ml) for 8 h. The reaction was monitored by NMR and continued until the alkene had disappeared. The reaction mixture was cooled, extracted with ether (3 x 50 ml), the extract dried (Na_2SO_4) and evaporated. The product was recrystallized from petroleum ether (0.85 g, 70%) mp 100-101 °C; ^1H NMR ($CDCl_3$) δ 1.76-2.65 (m, Adamantane H), 4.60 (br s, CHCl) 7.31 (s, C_6H_5). Anal. Calcd. for $C_{16}H_{29}Cl$: C, 77.85; H, 7.75. Found: C, 78.02; H, 7.79.

Attempted Synthesis of 1-Phenyladamantane-2-carboxlic acid via Grignard Synthesis. 1-Phenyl-2-bromoadamantane (2.25 g, 0.0077 mol), magnesium turnings (RMC-3, 99.98%; obtained from Reade Manufacturing Co., Inc., Lakehurst, N.J., 1.8 g, 0.075 g-atom) were placed in a two necked flask equipped with an efficient condenser and a nitrogen inlet tube. Anhydrous ether (dried over sodium metal) was added and the reaction initiated by adding 1,2-dibromoethane (0.25 ml) and the reaction mixture was refluxed gently (35-40 °C) for 12 h. Upon cooling, anhydrous CO_2 was passed through the mixture for 3 h. The reaction mixture was poured into ice-water (150 ml) containing HCl (5 ml). The organic layer was separated and the aqueous layer extracted with ether (2 x 50 ml). The combined extracts were extracted with 10% NaOH solution (3 x 50 ml). Neutralization of the basic solution with dil HCl, and upon extraction with ether (3 x 50 ml) did not yield any acidic material.

The neutral portion obtained by evaporation of ether (after sodium hydroxide treatment) gave a crystalline solid (1.5 g, 94%) mp 85-86 °C. The ^1H NMR and TLC of this corresponds to that of 1-phenyladamantane (lit.[22] mp 87-89 °C). The mass spectrum also showed that the product containined a small amount of a

minor product (M^+, 422); probably 1,1'-biadamantyl. No attempt was made to isolate this known hydrocarbon.

When the above reaction was carried out as above, but pouring the reaction mixture onto Dry-Ice, a 96% yield of 1-phenyladamantane was isolated. When ordinary magnesium turnings were used no reaction occurred but starting 1-phenyl 2-bromoadamantane was recovered in an almost quantitative yield.

Attempted Synthesis of 1-Phenyl-2-adamantanecarbonitrile

From 1-Phenyl-2-haloadamantane (Bromo or Chloro)

Reaction of 1-phenyl-2-bromoadamantane with KCN with or without phase transfer catalyst lead to the quantitative recovery of the starting material. No reaction took place even in presence of tetra-n-butyl ammonium bromide and the reaction mixture refluxed in toluene for 24 h.

From 1-Phenyladamantane-2-ol

Attempts made to replace hydroxy group directly by nitrile by treatment with Me_3SiCl[23] were also futile and starting material was recovered.

From 1-Phenyl-2-adamantyl-p-toluosulfonate

No 1-phenyl-2-adamantanecarbonitrile was obtained when 1-phenyl-2-adamantyl-p-toluosulfonate was treated with KCN in toluene in presence of a phase-transfer-catalyst (tetra-n-butylammonium bromide) at reflux temperature (24 h). The starting material was recovered (95%).

1-Phenyl-2-adamantanol. 4-Phenyl-4-protoadamantaneol prepared from 4-protoadamantane (2 g, 0.013 mol) was refluxed with formic acid (98%, 100 ml) for 30 min and the solution was evaporated in vacuo. 1-Phenyl-2-adamantyl formate was obtained ^{1}H NMR ($CDCl_3$) δ 1.76-2.56 (m, Ad H), 5.38 (br s, 2-H), 7.27 (br s, ArH), 7.98 (s, CHO) and was dissolved in acetone (160 ml) to be hydrolyze by refluxing with 1 N HCl (40 ml) for 2 h. After removal of volatile materials, in vacuo, the residue was extracted with ether (3 x 50 ml), and the ether extract

washed with water and dried (Na_2SO_4). After evaporation of ether, the solid was passed through a column of silica gel (100 g) and eluted with solvent mixtures containing an increasing concentration of ethylacetate in petroleum ether. Fractions eluted with 10% ethyl acetate provided pure 1-phenyl-2-adamantanol (2.1 g, 70% based on 4-protoadamantanone) mp 70-71 °C (lit.[8a] mp 70-72 °C); ^{1}H NMR (CCl_4) δ 1.09 (s, OH, exchangable with D_2O), 1.30-2.56 (m, AdH), 3.87 (br s, H-2), 7.24 (s, ArH).

1-Phenyl-2-adamantyl p-toluenesulfonate. 1-Phenyl-2-adamantanol 90.22 g, 0.001 mol) was dissolved in pyridine (3 ml) and cooled to 0 °C. Freshly purified p-toluenesulfonyl chloride (0.4 g, 0.002 mol) was added. After solution was affected, the mixture was placed in the refrigerator for 3 days. Long needles of pyridine hydrochloride separated. The reaction mixture was poured into ice-water (50 ml) and the crystalline solid filtered, washed well with water and dried. The product was recrystallized from pentane, mp 192-194 °C (lit.[8a] mp 198-200 °C). The yield was 0.31 g (75%); ^{1}H NMR ($CDCl_3$) δ 1.55-2.58 (m, AdH), 2.35 (s, CH_3) 6.90-7.36 (m, ArH).

1-Phenyl-2-adamantanone. Jones' reagent were prepared by mixing chromic oxide (1.3 g), conc. sulfuric acid (1.1 ml) and water (3.9 ml). One ml of this solution was added to a stirred solution of 1-phenyl-2-adamantanol (0.5 g, 0.0022 mol) in acetone (10 ml). After stirring at room temperature for 2 h, excess chromic acid was destroyed by the dropwise addition of aqueous methanol. The solution was concentrated, in vacuo, and water (100 ml) was added. The product was filtered and recrystallized from pentane to produce the ketone (0.45 g, 90%), mp 152-153 °C; (lit.[8a] mp 152-153 °C); ^{1}H NMR ($CDCl_3$) δ 1.69-2.69 (m, AdH), 7.28 (s, ArH); MS m/e 227 (9.7), 226 (M^+, 55), 198 (25), 156 (20), 155 (100), 142 (9), 129 (9), 118 (15), 115 (15), 91 (25).

1-Phenyl-2-adamantanecarbonitrile. To an ice-cold solution of tosylmethyl isocyanide (1.29 g, 0.0066 mol) in dry DMSO (7.5 ml) was added t-BuOK (1.77 g, 0.0158 mol) in one portion. After stirring for 5 min under N_2, methanol (0.25 ml) was added, followed by 1-phenyl-2-adamantanone (0.5 g, 0.0022 mol). The reaction mixture was stirred for 1 h at room temperature and then 70 h at 45 °C in an atmosphere of nitrogen. The mixture was diluted with water (20 ml), acidified with 2 N HCl to pH 6 and extracted with ether (3 x 50 ml). The ether extracts were washed well with water and dried (Na_2SO_4). Solvents were evaporated and the residue chromatographed on silica gel (40 g). 1-Phenyl-2-adamantanecarbonitrile (0.35 g, 72%) was eluted by benzene, mp 111-112 °C. Recrystallization from aqueous ethanol raised the mp to 112-113 °C; TLC, R_f 0.7 ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.61-2.58 (m, AdH), 3.15 (br s, H-2), 7.34 (br s, ArH); MS m/e 239 91), 238 (12), 237 (M^+, 64), 156 (18) 155 (100), 119 (10), 118 (57), 91 (22); IR (KBr) 2240 cm^{-1} (ν_{CN}). Anal. Calcd. for $C_{17}H_{19}N$: C, 86.03; H, 8.06; N, 5.90. Found: C, 85.66; H, 8.23; N, 5.64.

The last benzene fraction from the column consisted of tosyl oxazole (0.2 g), mp 155-156 °C (lit.[12] mp 156-157 °C) whose ^1H NMR spectrum corresponded to the one in the literature.

Reduction of 1-Phenyl-2-adamantanecarbonitrile

Method A: With lithium aluminum hydride. A suspension of lithium aluminum hydride (0.42 g, 0.011 mol) in dry tetrahydrofuran (20 ml) was stirred (N_2 atmosphere) while a solution of 1-phenyl-2-adamantanecarbonitrile (2.37 g, 0.01 mol) in THF (15 ml) was added (30 min). The mixture was heated under reflux for 3.5 h, cooled, and decomposed with water (1.5 ml), followed by sodium hydroxide (10%, 2.5 ml). Solids were filtered off and were washed with THF (2 x 10 ml). The THF filtrate was dried (Na_2SO_4) and evaporated, in vacuo. The residue was dissolved in ether, filtered to free it from some powdery solid (0.3 g, mp 210 °C).

Characterization of this product is still under investigation. Dry HCl gas was passed in to an ethereal solution of the amine. The solid which precipitated was filtered, washed several times with ether and recrystallized from aqueous ethanol to yield the salt (0.12 g, 51%), mp 275-278 °C (dec. turns light brown at 260 °C); ^{1}H NMR (CF_3COOH) δ 1.48-2.29 (m, AdH), 3.49 (m, CH_2N), 7.38 (m, ArH). Anal. Calcd. for $C_{34}H_{43}ClN$: C, 81.31; H, 8.83; N, 2.78; Cl, 7.05. Found: C, 82.03; H, 8.70; N, 2.73; Cl, 6.82.

A small amount of the pure amine hydrochloride (0.1 g) was suspended in water and neutralized by 10% sodium hydroxide solution. Extraction with ether yielded the amine as gum which solidified upon standing (2 days); ^{1}H NMR (CCl_4) δ 1.25-2.40 (m, AdH), 2.77 (M, CH_2N), 7.16 (m, ArH); MS m/e 464 (1) 463 (2, 3), 253 (19), 252 (100), 240 (1), 223 (3), 155 (9), 129 (4), 117 (4), 115 (3), 105 (5).

Method B: With Borane-dimethylsulfide. An oven-dried 3-necked flask (100 ml capacity) was equipped with a septum-capped graduated dropping funnel, a magnetic stirring bar, Vigreux column attached to a distillation head and condenser with graduated cylinder as the receiver. The outlet is connected to a mercury-bubbler. A nitrogen atmosphere was maintained throughout the reaction. 1-Phenyl-2-adamantanecarbonitrile (3.54 g, 0.015 mol) was dissolved in boiling tetrahydrofuran (7 ml, distilled over LAH). Borane-dimethyl sulfide (1.65 ml, 0.0165 mol, 10 M solution in hexane, purchased from Aldrich) was transferred directly from the bottle to the dropping funnel through a double ended needle, using nitrogen pressure and was added dropwise to the reaction mixture (10 min). Dimethyl sulfide (1.2 ml) was distilled off and collected in the receiver. After 0.5 h, the reaction mixture was cooled to room temperature and HCl (6 N, 10 ml) was added dropwise. Hydrogen evolved and the reaction mixture was heated under reflux for 0.5 h. The solution was cooled, neutralized by adding NaOH (10%) and

was extracted with chloroform (3 x 100 ml), washed well with water and dried (Na_2SO_4). After solvents have been evaporated, the residue was dissolved in methanol and dry HCl gas passed through the solution. Solvents were evaporated, in vacuo, and the residue diluted with ether. The solid so obtained was filtered and washed several times with ether. The product was recrystallized from aqueous ethanol, mp 279-282 °C (dec.). It weighed 3.1 g (82%); ^1H NMR, mass spectrum and elemental analyses corresponded to the salt obtained from the lithium aluminum hydride reduction in Method A.

The amine hydrochloride was sparingly soluble in DMSO but moderately soluble in methanol at room temperature. The amine was refluxed with acetic anhydride and an acetyl derivative was obtained and its structure is under investigation.

1-Phenyl-2-adamantanecarboxamide. 1-Phenyl-2-adamantanecarbonitrile (0.24 g, 0.001 mol) was dissolved in methanol (10 ml) and dimethyl sulfoxide (0.2 ml) was added followed by H_2O_2 (11%, 1 ml) and NaOH (0.2 M, 0.2 ml). The reaction mixture was heated (50 °C) and monitored by TLC on a silica gel plate using $CHCl_3$ 95% C_2H_5OH (18:1, R_f = 0.49). Starting material was virtually absent from the TLC plate after 6 h. After removal of solvents, in vacuo, water (20 ml) was added and the product filtered, and washed with water. Recrystallization from methanol afforded long needle-shaped crystals (0.20 g, 78%) mp 160-161 °C; ^1H NMR ($CDCl_3$) δ 1.52-2.84 (m, AdH), 4.92 (br s, $CONH_2$), 7.34 (s, ArH); IR (KBr) showed absorption at 1656 (C=O stretching) and 3200 cm^{-1} (N-H stretching). Anal. Calcd. for $C_{17}H_{21}NO \cdot H_2O$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.95; H, 8.66; N, 5.13.

1-Phenyl-2-adamantylmethylamine hydrochloride. A solution of 1-phenyl-2-adamantanecarboxamide (0.51 g, .002 mol) in anhydrous THF (30 ml) was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.4 g, 0.01 mol)

in THF (20 ml). The reaction mixture was refluxed for 18 h, cooled to 0 °C, and water (0.4 ml), NaOH (10%, 1.2 ml) and again water (0.4 ml) were added. Solids were filtered off, washed with ether, the combined organic filtrate was dried (Na_2SO_4). After solvents were evaporated, the residue was mixed with anhydrous ether and filtered to remove insoluble materials. Dry HCl gas was passed through the ether filtrate and the amine hydrochloride was filtered, washed with ether. The product was recrystallized from aqueous ethanol to yield 0.4 g (72%) mp 300-302 °C (dec, starts turning yellow 265 °C); ^{1}H NMR ($CDCl_3$) δ 1.54-2.20 (AdH), 2.50 (CH_2N), 7.29 (s, ArH), 8.03 (br s, $\overset{+}{N}H_3$); MS m/e 22 (M$^+$ + 1, 7), 241 (M$^+$, 36), 224 (80), 163 (41), 156 (22), 155 (94), 129 (29), 106 (56), 91 (100). Anal. Calcd. for $C_{17}H_{24}ClN$: C, 73.49; H, 8.70; N, 5.04. Found: C, 73.09; H, 8.64; N, 4.75.

4-Epoxymethyleneprotoadamantane. The preparation represents an adaptation of the literature methods. To solution of 4-protoadamantanone (3.8 g, 0.025 mol) and trimethylsulfoxonium iodide (8.25 g, 0.037 mol) in dry dimethyl sulfoxide (50 ml) was added sodium hydride (0.75 g, 0.031 mol) under a stream of nitrogen. The mixture was stirred at 50-55 °C for 18 h, cooled to 10 °C, and poured onto ice-water (100 ml). The product was extracted with carbon tetrachloride and the extract was washed with water and dried (Na_2SO_4) evaporated in vacuo to give a waxy solid, mp 60-64 °C; (lit.[8b,16] mp 62-64 °C); ^{1}H NMR ($CDCl_3$) δ 1.56-2.18 (m, AdH), 2.60 (s, suggested for the CH_2 of the endo isomer, AB quartet centered about 2.60 for the exo isomer, see structure **31.**

2. **Syntheses Leading Towards (1-Aryl-3-adamantanemethylamines and Related 2-Mercaptoacetamidines**

1- or 2-Thienyl-3-adamantanecarboxylic Acid. To a boiling vigorously stirred solution of 1-bromo-3-adamantanecarboxylic acid (5.2 g, 0.02 mol) in thiophene (30 ml), was added stannic chloride (5.2 g, 0.02 mol) during a period of 25 min. The reaction mixture was refluxed for another 30 min, cooled and poured onto ice-water (100 ml) containing conc. HCl (6 ml). The organic layer separated and the aqueous layer extracted with benzene (2 x 25 ml). The combined organic layer was washed well with water and treated with sodium hydroxide solution (10%, 75 ml) which had been saturated with sodium chloride. The sodium salt of the acid separated which was filtered and washed with saturated solution of sodium chloride. The salt was suspended in water (50 ml) and acidified by the addition of conc. hydrochloric acid. The acid was filtered, and washed with water and dried (mp 100 ^{o}C). The yield was 2.5 g (47%). GC analysis of its methyl ester (prepared for analysis from the acid and diazomethane) using an OV-225 Gas Chrom-Q column, showed a mixture of two isomers in the ratio of 2:1. The crude mixture of acid was converted into the corresponding amides which were partially separated by preparative liquid chromatography. A small amount of the 1- 2-thienyl-3-adamantanecarboxamide (150 mg) on boiling with 10% sodium hydroxide solution (5 ml) for 18 h gave the corresponding acid (120 mg), mp 140-141 ^{o}C; ^{1}H NMR ($CDCl_3$) at 60 MHz δ 1.74-2.51 (m, adamantane protons), 6.84-7.25 (m, thiophene protons), 11.37 (br s, CO_2H). Anal. Calcd. for $C_{15}H_{18}O_2S$: C, 68.66; H, 6.92. Found: C, 68.29; H, 6.91.

1-(2-Thienyl)-3-adamantanecarboxamide. A mixture of the crude carboxylic acids prepared above (4.25 g, 0.016 mol), phosphorous pentachloride (3.37 g, 0.016 mol) and carbon tetrachloride (10 ml) was refluxed for 1 h. volatile materials were distilled in a flash evaporator and the residue treated thrice with carbon tetra-

chloride (20 ml) and evaporated in vacuo. The residue was dissolved in anhydrous tetrahydrofuran and it was added dropwise to a stirred ice-cold 28% ammonium hydroxide solution (100 ml). After stirring overnight, the solid (3.5 g, 82%) was filtered and washed with water.

Complete separation of 3-(2- and 3-thienyl)-3-adamantanecarboxamides, (3d and 3e) by medium pressure column chromatography or thin layer chromatography (silica gel or alumina) proved difficult. For example, TLC on 0.25 mm silica gel with a fluorscent indicator, Polygram^{R}, SIL G/UV$_{254}$ (Brinkmann Instruments Inc.) gave only one spot, detected by UV light, R_f = 0.45 (chloroform-95% ethanol 9:1). Preparative liquid chromatography on a Waters^{TM} Auto-500A Chromatograph, and a Prep Pak^{R} Silica (5.7 x 30.0 cm) column, flow rate 250 ml/min (refractive index detector) separated 0.120 g of 3d from a 1.5 g mixture of 3d and 3e using ethyl acetate-chloroform (3:1) as solvent; mp 120-122 °C 180 MHz ^{1}H NMR ($CDCl_3$) δ 5.85 (d, $CONH_2$), 6.75 (dd, H-3 of thiophene), 6.84 (dd, H-4 of thiophene), 7.05 (dd, H-5 of thiophene) $J_{4,5}$ = 5.1, $J_{3,4}$ = 3.6, $J_{3,5}$ = 1.2 Hz; MS 263 (5), 262 (14), 261 (M^+, 66), 217 (97), 161 (30) 149 (100). Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.92; H, 7.32; N, 5.36; S, 12.25. Found: C, 68.68; H, 7.32; N, 5.36; S, 12.12.

1-(2-Thienyl)-3-adamantanemethylamine Hydrochloride. The pure 1-(2-thienyl)-3-adamantanecarboxamide (2.4 g, 0.0091 mol) dissolved in anhydrous tetrahydrofuran (40 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.75 g, 0.047 mol) in anhydrous tetrahydrofuran (150 ml). The reaction mixture was refluxed for 24 h and worked up as usual by cooling and adding water (1.75 ml), sodium hydroxide (10%, 5.2 ml) and again water (1.75 ml). Solids were filtered off and washed with ether. The combined ether filtrate was dried (Na_2SO_4) and the solvent evaporated and residue taken up in anhydrous ether, filtered to remove some insoluble material.

Upon bubbling anhydrous hydrogen chloride gas through the ether solution, the amine hydrochloride precipitated. It was filtered, washed with water and recrystallized from aqueous ethanol, mp 240-245 °C. The yield was 2.1 g (81%); ^{1}H NMR (DMSO-d_6) 1.58 to 1.80 (m, methylene protons of adamantane) 2.17 (br s, bridgehead protons) 2.59 (br s, CH_2N) 6.9 to 7.5 (m, thiophene protons) 8.01 (br s, $\overset{+}{N}H_3$); MS 249 (3) 248 (9) 247 (M^+-HCl, 48) 218 (100), 217 (62), 135 (22), 134 (52), 133 (23). Anal. Calcd. for $C_{15}H_{22}ClNS$: C, 63.46; H, 7.81; N, 4.93. Found: C, 63.06; H, 7.77; N, 4.87.

N-[1-(2-Thienyl-3-adamantanemethyl]-2-chloroacetamidinium Hydrochloride. Chloroacetonitrile (0.58 g, 0.0077 mol) was added to a solution of sodium methoxide (prepared from 0.0178 g of sodium in 6.2 ml of methanol) and stirred at room temperature for 1 h. A solution of 1-(2-thienyl)-3-adamantanemethylamine hydrochloride (2.2 g, 0.0077 mol) in methanol (30 ml) was added and pH adjusted to 4 by adding methanolic HCl. The pH was tested by means of wet ALKACID^R Test paper (Fischer Scientific Co.). The reaction mixture was stirred at room temperature for 2 h. Solvents were evaporated, in vacuo, at room temperature and the residue was triturated with ether. The colorless white powder was filtered, washed with ether and recrystallized from aqueous ethanol to give 2.3 g (92%) of the chloracetamidine hydrochloride, mp 216-218 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.6 to 1.76 (m, methylene protons of adamantane) 2.11 (s br, bridgehead protons), 3.18 (s, CH_2N), 4.58 (s, CH_2Cl), 6.88 to 7.36 (m, aromatic protons) and 8.61 (s br, $\overset{+}{N}H_3$). Anal. Calcd. for $C_{17}H_{24}Cl_2N_2S \cdot 1\ H_2O$: C, 54.08; H, 6.94; N, 7.42. Found: C, 54.40; H, 6.95; N, 7.19.

Sodium S-{N-[3-(2-Thienyl)-1-adamantanemethylcarboxamidinium methyl]} Phosphorothioate. A solution of N[3-(2-thienyl)-1-adamantylmethyl-α-chloroacetamidine]hydrochloride (0.50 g, 0.0014 mol) in aqueous ethanol (50%, 10 ml) was added to a solution of freshly prepared trisodium phosphorothioate (0.37 g, 0.0020

mol) dissolved in water (5 ml). The mixture was stirred under nitrogen for 30 min. The precipitate was filtered and recrystallized from ethanol-ether, mp 118-120 °C (dec.). It weighed 0.48 g (81.3%); ^{1}H NMR (CD_3COOD) δ 1.67-2.10 (m, adamantane protons), 3.15 (s, CH_2N), 3.87 (d, CH_2-S-P, J_{P-H} = 17 Hz), 6.85 to 7.25 (m, thiophene protons). Microanalytical data was difficult to obtain. The best values were as follows. Anal. Calcd. for $C_{17}H_{24}N_2O_3PS_2Na \cdot 6H_2O$: C, 38.49; H, 6.84; N, 5.28; S, 12.06. Found: C, 38.27; H, 5.58; N, 5.20; S, 12.04.

N-[1-(2-Thienyl)-3-adamantanemethyl]-2-mercaptoacetamidinium Chloride. A solution of N-[1-(2-thienyl-3-adamantanemethyl]-2-chloroacetamidine hydrochloride (2.14 g, 0.006 mol) in 50% ethanol (20 ml) was added to a solution of sodium phosphorothioate (1.08 g, 0.006 mol) in water (10 ml) and the mixture was stirred at room temeprature for 30 min. After that period, 6 N HCl (15 ml) was added and the reaction mixture was heated at 85-90 °C for 20 min. Upon cooling, white crystals separated which were filtered and recrystallized from aqueous ethanol. The yield was 1.6 g (74.7%) mp 185-187 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.60-1.80 (m, CH_2's of adamantane ring), 2.11 (s br, bridgehead protons), 3.09 (d, CH_2N), 3.54 (s, CH_2S), 6.89 to 7.38 (m, thiophene protons) 8.93, 9.49 and 9.78 (br s, NH-C=$\overset{+}{N}H_2$); IR (Nujol) shows δ (C=NH_2) and ν (C=N) at 1690 and 1650 cm^{-1} respectively. Anal. Calcd. for $C_{17}H_{25}ClN_2S_2$: C, 57.19; H, 7.06; N, 7.84; S, 17.94. Found: C, 57.21; H, 6.94; N, 7.39; S, 17.48.

3. Approaches to the 1-Aryl-4-adamantanemethylamine System

1-Bromo-4-adamantanone. t-Butyl bromide (2 ml) was added dropwise to a stirred mixture of anhydrous aluminum bromide (44.0 g, 0.165 mol), adamantanone (5 g, 0.033 mol) and bromine (10 ml, 0.195 mol) placed in a 100 ml thick-walled

round bottom flask. The flask was closed with a teflon stopper and the reaction mixture was stirred at room temperature for 3 days. After allowing hydrogen bromide to escape, the viscous reaction mixture was poured onto crushed ice and extracted with methylene chloride (5 x 100 ml). The organic layer was decolorized by shaking with 5% sodium bisulfite solution, washed with water (200 ml) and 5% sodium bicrbonate solution (150 ml), dried over magnesium sulfate. Evaporation in vacuo resulted in an oil which was passed through a column 96 cm x 30 cm) of silica gel (300 g, 50-100 μ) and eluted with 3% acetone in petroleum ether. The combined fractions containing the desired product on evaporation gave the bromo ketone, 3.2 g (42%, lit.[18] yield 72-80 %) which was further purified by crystallization from petroleum ether (charcoal), mp 150-152 °C (lit.[18a] mp 154 °C); ^{1}H NMR ($CDCl_3$) δ 2.58 (br s, Ad protons), 2.26 (m, H-7), 2.06 (br s, H-10).

In later experiments following personal correspondence with the authors about the publishd procedure[18b] yields could be improved to (68-78%) by using $AlBr_3$ (80 g, 0.3 mol) bromine (15 ml, 0.29 mol) and t-BuOH (1 ml) for 5 g of adamantanone.

1-(4-Methylphenyl)-4-adamantanone. Aluminum chloride (2 g, 0.015 mol) was gradually added to a stirred solution of 1-bromo-4-adamantanone (2.1 g, 0.009 mol) in toluene (20 ml) and the reaction mixture refluxed for 1 h, poured onto ice-water (150 ml) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic phase was washed with water (150 ml) dried (Na_2SO_4) and evaporated, in vacuo. The residue was recrystallized from petroleum ether to furnish crystals (2.2 g, 90%) mp 65-66 °C; ^{1}H NMR ($CDCl_3$) δ 2.08-2.32 (m), 2.65 (br s), (Ad Hs), 2.32 (s, CH_3), 7.19 (br s, ArH). MS m/e 242 (2), 241 (M^+, 15), 182 (33), 171 (16), 170 (30), 169 (100), 132 (22), 129 (24), 128 (24), 105 (70). Anal. Calcd. for $C_{17}H_{21}O$: C, 84.58; H, 8.77. Found: C, 84.29; H, 8.37.

1-(4-Methylphenyl)-4-adamantanecarbonitrile. 1-(4-Methylphenyl)-4-adamantanone (2.41 g, 0.01 mol) and tosylmethyl isocyanide (2.5 g, 0.013 mol) was dissolved in dry 1,2-dimethoxy ethane (DME, 35 ml) and absolute ethanol (1 ml) was added and the mixture cooled to 5 to 10 °C. Solid t-BuOK (2.8 g, 0.024 mol) was added in small portions while stirring the solution around 5-10 °C. Stirring was continued for 0.5 h without cooling and then for 3 h at 35-40 °C. The suspension which was formed was cooled to room temperature with stirring. The precipitate was filtered, washed with DME. The combined filtrate was evaporated in vacuo and passed through a column of silica gel (80 g) and was eluted with benzene:petroleum ether (1:1) to give a dense oil which shows a single spot on TLC (silica gel) plate in chloroform (R_f, 0.56); GC (OV 17 at 220 °C) showed the product to be a mixture, probably the two isomers (syn and anti). Upon standing a long time, needle shaped crystals separated which were recrystallized from acetone, mp 108-110 °C, yield 1.6 g (62%); ^{1}H NMR ($CDCl_3$) δ 1.62-2.81 (m, AdH), 2.32 (s, CH_3), 7.05 (s, ArH). MS m/e 253 (M^+ + 2, 2), 252 (M^+ + 1, 17), 251 (M^+, 82) 169 (100), 132 (76), 105 (23), 91 (24). IR (Nujol) shows C N stretching at 2224 cm^{-1}. Anal. Calcd. for $C_{18}H_{21}N$: C, 86.00; H, 8.42; N, 5.57. Found: C, 86.29; H, 8.29; N, 5.54.

1-(4-Methylphenyl)-4-adamantylmethylamine Hydrochloride. 1-(4-Methylphenyl)-2-adamantanone (1.26 g, 0.005 mol) dissolved in dry THF (9 ml) was added dropwise during a period of 0.5 h to a stirred suspension of lithium aluminum hydride (0.23 g, 0.0055 mol) in dry THF (40 ml) in an atmosphere of nitrogen. The mixture wsa heated under reflux for 2.5 h, cooled and treated with water (0.75 mol) and NaOH (10%, 0.125 ml). After filtering the precipitate, the solid washed with ether, the combined filtrate was dried (Na_2SO_4). Solvents were removed, in vacuo, and the residue taken up in anhydrous ether, filtered dry HCl gas was passed into the filtrate. The amine hydrochloride which had precipitated was filtered, washed with ether and was recrystallized from ethanol-ether, (0.9 g, 62%), mp 240-245 °C;

^{1}H NMR (DMSO-d_6) δ 1.59-2.00 (m, Ad Hs), 2.29 (s, CH_3), 2.93 (m, CH_2N), 7.14 (s, 7.14), 8.19 (br s, $\overset{+}{N}H_3$). MS pending. Anal. Calcd. for $C_{18}H_{26}NCl$: C, 74.07; H, 8.97; N, 4.79. Anal. pending for C, H. Found: C, 4.79.

4. **N-[4-(1-Adamantylbenzyl]-2-mercaptoacetamidine and Derivatives.**

1-(p-Bromophenyl)adamantane. 1-Bromoadamantane (33 g, 0.15 mol) was dissolved in bromobenzene (255 ml) and added dropwise to a suspension of ferric chloride (9.3 g) in bromobenzene (160 ml). The reaction mixture was refluxed for 3.5 h, then cooled and poured into cold water. The organic layer was separated and aqueous layer extracted several times with benzene. The combined organic layer was washed several times with water, dried ($CaCl_2$) and solvents were evaporated in vacuo. The residue (22 g) was chromatographed on alumina (600 g). Elution with petroleum ether provided 19.0 g (60%) of the product, mp 100-101 °C (lit.[22] mp 101-102 °C); ^{1}H NMR ($CDCl_3$) δ 1.81-2.08 (adm H), 7.21, 7.41 (AA'BB' pattern of aromatic protons).

4-(1-Adamantyl)benzoic Acid. A three necked flask was equipped with a reflux condenser, a stirrer, a dropping funnel and a nitrogen inlet tube. Magnesium turnings (0.96 g, 0.04 g-atom) were placed in the flask and a slow current of nitrogen was passed throughout the experiment. A solution of methyl iodide (0.1 ml) in anhydrous THF (20 ml) was added. After the reaction had initiated and THF started to boil gently, the mixture was commenced to stir. A mixture of 1-(4-bromophenyl)admanatane (6.0 g, 0.02 mol) and methyl iodide (2.82 g, 0.02 mol) in THF (30 ml) was added at such a rate that gentle boiling continued (75 min). The reaction mixture was then refluxed for another 2 h, cooled and poured onto crushed Dry-Ice (150 g). After 1 h, dil. HCl (5 ml) was added and the mixture extracted

with ether (3 x 100 ml). Ether extracts were washed with water (100 ml) and then treated with 10% NaOH (5 x 50 ml). The sodium hydroxide solution was separated, boiled to remove dissolved ether, cooled and neutralized by adding dil. HCl. The acid was filtered, washed with water and recrystallized from ethyl acetate, mp 306-307 °C (lit.[24,25] mp 308-309, 316 °C). The yield was 3.4 g (66%); ^{1}H NMR (DMSO-d_6) δ 1.74-2.01 (AdH), 7.46, 7.89 (AA'BB', ArH).

4-(1-Adamantyl)benzamide. A mixture of 4-(1-adamantyl)benzoic acid (2.0 g, 0.0078 mol) phosphorous pentachloride (1.62 g, 0.0078 mol) in carbon tetrachloride (40 ml) was refluxed for 1 h. Solvents were evaporated, in vacuo, and the residue treated with carbon tetrachloride (20 ml) and reevaporated. This procedure was repeated twice to remove any volatile phosphorous halides. The residue was taken up in anhydrous benzene and added dropwise to stirred ammonium hydroxide (28%, 50 ml) at 0 °C. The mixture stirred for 8 h, extracted with ether (3 x 100 ml), the ether phase washed with water and dried (Na_2SO_4). The product was recrystallized from ethanol to yield 1.5 g (75%) of amide, mp 200-202 °C; ^{1}H NMR ($CDCl_3$) δ 1.78-2.07 (m, AdH), 5.90 (br s, $CONH_2$), 7.42, 7.77 (m, AA'BB', ArH). Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.97; H, 8.29; N, 5.48. Found: C, 79.94; H, 8.31; N, 5.23.

4-(1-Adamantyl)benzylamine Hydrochloride. 4-(1-Adamantyl)benzamide (7.1 g, 0.0278 mol) was reduced as usual in a 3-necked flask fitted with condenser, dropping funnel and $CaCl_2$ tube (see prep. of **12d**), using lithium aluminum hydride (5.34 g, 0.139 mol) in anhydrous tetrahydrofuran (350 ml). The amine was taken up in ether and treated with HCl gas. The hydrochloride was filtered, washed with ether and recrystallized from aqueous ethanol. The yield was 6.0 g (78%), mp 304-305 °C; ^{1}H NMR (DMSO-d_6) δ 1.77-2.02 (m, adamantane protons), 3.95 (s, CH_2N) 7.39 (s, aromatic protons) 8.22 (s br, $\overset{+}{N}H_3$). Anal. Calcd. for $C_{17}H_{24}ClN$: C, 73.46; H, 8.71; N, 5.04. Found: C, 73.47; H, 8.80; N, 4.92.

N-[4-(1-Adamantyl)benzyl]-2-chloroacetamidinium Hydrochloride. This salt was obtained in 84% (3.0 g) yield from 4-(1-adamantyl)benzylamine hydrochloride (2.77 g, 0.01 mol) by the standard procedure. Starting from chloroacetonitrile (0.754 g, 0.01 mol) and sodium methoxide (prepared from 0.023 g of sodium in 8 ml of methanol) the amidine was prepared as described for the preparation of 7 (Ar = 2-thienyl). After recrystallization from aqueous ethanol, the product melted at 148-150 °C; ^{1}H NMR (DMSO-d_6) δ 1.77-2.01 (m, adamantane ring protons), 4.50 (s, CH_2N, and $CH_2C_6H_5$), 7.34 (s, ArH), 9.34 (s br, NH-C=NH_2). Anal. Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.55; H, 7.41; N, 7.92. Found: C, 64.34; H, 7.15; N, 7.49.

Sodium S-{ N-[4-(1-Adamantyl)benzyl] carboxamidinium Methyl } phosphorothioate. A solution of N-[4-(1-adamantyl)benzyl-]2-chloroacetamidinium hydrochloride (0.50 g, 0.0014 mol) was dissolved in aqueous ethanol (50%, 15 ml) and mixed with a solution of trisodium thiophosphate (0.25 g, 0.0014 mol) in water (5 ml). The mixture was stirred for 30 min in an atmosphere of nitrogen. The solid was filtered, washed with little water (1 ml) and ether, and recrystallized from ehtanol-ether, mp 120-121 °C. The yield was 0.4 g (75%); ^{1}H NMR (CD_3CO_2D) δ 1.85-2.0 (m, adamantane protons), 3.88 (d, CH_2-S-P, J_{CH_2-P} 15.4 Hz), 4.53 (s br, CH_2N) and 7.36 (s, aromatic protons). The best analytical data were as follows: Anal. Calcd. for $C_{19}H_{26}N_2SPO_3Na \cdot 2H_2O$: C, 50.44; H, 6.68; N, 6.19. Found: C, 50.15; H, 6.26; N, 5.47.

N-[4-(1-adamantyl)benzyl]carboxamidino)methyl disulfide dihydrochloride. A solution of N-[4-(1-adamantyl)benzyl]-2-chloroacetamidinium hydrochloride (2.5 g, 0.007 mol) in aqueous ethanol (50%, 20 ml) was added to a solution of trisodium thiophosphate (1.8 g, 0.010 mol) in water (10 ml) and the mixture stirred for 30 min (N_2). Then, 6 N HCl (15 ml) was added and mixture heat at 90-95 °C for 20 min (N_2). The solid which had separated turned gummy upon filtration and attempts to crystallize this semi-solid from ethanol-ether proved futile. The crude mercaptan

was dissolved in methanol (10 ml) and hydrochloric acid (1:1, 5 ml) and was oxidized by 3% H_2O_2 (2.4 ml), added dropwise (1.5 h). After another 1.5 h at room temperature, the mixture was concentrated, in vacuo, the solid filtered and washed with water (4 ml). After recrystallization from ethanol-ether, the product weighed 2.1 g (86%), mp 255-260 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.74-2.03 (m, adamantane protons), 3.94 (s, CH_2-S), 4.54 (d, CH_2N), 7.35 (s, aromatic protons), 9.23, 9.72 and 10.46 (singlets, br, NH-C=NH_2). IR (Nujol) shows δ (C=NH_2) and ν (C=N) at 1690 and 1650 cm^{-1} respectively. Anal. Calcd. for $C_{38}H_{52}Cl_2N_4S_2$: C, 65.19; H, 7.49; N, 8.00; S, 9.15. Found: C, 65.00; H, 7.49; N, 7.53; S, 9.04.

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